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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/516,310	03/01/2000	Yao-Zhong Lin	22000.0021U2	3622

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EXAMINER	
LOEB, BRONWEN	

ART UNIT	PAPER NUMBER
1636	15

DATE MAILED: 06/03/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/516,310	LIN ET AL.	
	Examiner	Art Unit	
	Bronwen M. Loeb	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 February 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6-26,32 and 33* is/are pending in the application.

4a) Of the above claim(s) *16-26, 32 and 33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 March 2000* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☐ Notice of References Cited (PTO-892)
2)☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *2* .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

DETAILED ACTION

This action is in response to the communication filed 11 February 2002.

Claims 6-26, 32 and 33 are pending.

Election/Restrictions

1. Applicant's election with traverse of Group II, claims 6-10, in Paper No. 14 is acknowledged. The traversal is on the ground(s) that there is not a serious burden to examine all the claims. Applicant argues that the restriction groups in total constitute only two classes and three subclasses and therefore there is no additional burden to examine all the claims together. The restriction has been reconsidered and Groups II through V, claims 6-15, have been rejoined and Groups VI-VIII, claims 16-22, have been rejoined; this is also consistent with the restriction originally made in parent 08/258,852, now abandoned and the claims examined and allowed in previous parents.

After rejoinder, the groups consist of:

Group I, claim 32

Group II, claims 6-15 (elected)

Group III, claims 16-22

Group IV, claims 23-25

Group V, claim 26

Group VI, claim 33.

2. Applicant's argument is not found persuasive with respect to the remaining Groups because the two classes and three subclasses encompassed by these claims

include over 6000 patents. Furthermore, as set forth in the previous action, the burden to search these groups is not solely based on classification. The burden is also based on the different search required. For instance, the methods of rejoined Groups II, III, IV and V each require different searches. For instance, the method of Group III requires searching cell growth and cell growth regulation, which is not required by the other groups. Group IV requires a search of genes controlled by transcription factor NF-KB and inhibition of the expression of those genes, which is not required by the other groups. Therefore, burden has been established for the restriction groups.

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 16-26, 32 and 33 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Information Disclosure Statement

4. The reference listed as "Delli-Bovi et al, Cell 50:3206-3142" could not be located in parent file 08/258,852. Furthermore, in attempting to obtain the reference, it was found that Volume 50 of Cell does not does not have pages 3206-3142. Therefore, it is believed there is an error in the citation. However, if Applicant provides a copy of the cited reference, it will be considered without a fee.

Drawings

5. Applicant's attention is drawn to the attached Draftsperson's Patent Drawing Review, Form 948.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 6-15 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction of guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

The present claims are very broad. Claim 6 encompasses a method of importing any biologically active molecule into any cell in a subject by administering a complex comprising the molecule linked, covalently or non-covalently, to any importation competent signal peptide. Claim 11 encompasses a method of importing any

biologically active molecule into the nucleus of any cell in a subject by administering a complex comprising the molecule linked, covalently or non-covalently, to any importation competent signal peptide and a nuclear localization peptide.

The nature of the invention is a method of importing a biologically active molecule into a cell or a cell nucleus of a subject. The only use disclosed in the specification for this method is as a method of treatment. See for instance p. 1, lines 19-20 and 24, p. 3, lines 9-17 and p. 19, line 10- p. 20, line 7. The biologically active molecule may be a nucleic acid (see also p. 19, lines 7-17). Delivery of a nucleic acid to a cell in vivo for therapeutic purposes is gene therapy. Therefore, the claims encompass gene therapy.

An analysis of the prior art as of the effective filing date of the present application shows the complete lack of documented success for any treatment based on gene therapy. In a review on the current status of gene therapy, both Verma et al (Nature (1997) 389:239-242) and Palù et al (J. Biotechnol. (1999) 68: 1-13) state that despite hundreds of clinical trials underway, no successful outcome has been achieved. See Verma et al, p. 239, 1st paragraph; Palù et al, p. 1, Abstract. The continued, major obstacles to successful gene therapy are gene delivery and sustained expression of the gene. Regarding non-viral methods for gene delivery, Verma et al indicates that most approaches suffer from poor efficiency and transient expression of the gene (p. 239, col. 3, 2nd paragraph). Likewise, Luo et al (Nature Biotechnology (2000) 18:33-37) indicates that non-viral synthetic delivery systems are very inefficient. See p. 33, Abstract and col. 1, 1st and 2nd paragraphs. While all three references indicate the promise of gene

therapy, it is still a technique of the future and advancements in our understanding of the basics of gene delivery and expression must be made before gene therapy becomes a predictable and reliable technique. See Verma et al, p. 242, col. 2-3; Palù et al, pp. 10-11; Luo et al , p. 33, col. 1, 1st paragraph.

The relative skill of those in the art of gene therapy is high.

The area of the invention is unpredictable. As discussed above, the method of in vivo or ex vivo gene therapy is highly complex and unpredictable. The skilled artisan at the time the present invention was made recognized the difficulty of achieving sufficient heterologous gene expression to induce any therapeutic effect. Thus, the effectiveness of a potential new delivery system, such as linking the nucleic acid to an importation signal peptide, cannot be predicted in the absence of in vivo testing for a therapeutic effect.

The present specification provides little or no guidance to support the claimed invention for gene therapy applications. The specification discloses no specific therapeutic molecules and specific diseases to which the claimed process can be applied except to provide the CFTR gene to cystic fibrosis patients (p. 19, line 12-13). There is no direction provided as to how to overcome the obstacle to gene therapy recognized by leaders in the field, i.e. low efficiency of gene delivery and transient gene expression. Indeed, there is no specific direction as how to target the complex to any specific targeted cell, other than a list of routes of administration (p. 8, lines 2-15).

No working examples are disclosed in which a biologically active molecule linked to an importation signal peptide or linked to both an importation signal peptide and a

nuclear localization signal is imported into a cell, or the nucleus of a cell, in a subject. All of the working examples use tissue culture cell lines. There are no in vivo examples.

The quantity of experimentation necessary to carry out the claimed invention is high as the skilled artisan could not rely on the prior art or the present specification to teach how to use the claimed methods. In order to determine how to use the method to treat a condition, one of skill in the art would have to determine what effect exogenous transgene expression would have in any cell type, whether the effect could be exploited for treatment of a disease, how to deliver the given nucleic acid to the appropriate target cells with specificity and efficiency, and how to get sufficient expression to induce at least some therapeutic effect. With regard to all the other biologically active molecules claimed, one would have to determine how to direct/target the complex to the targeted cell type efficiently and whether a sufficient quantity of the complex is taken up by the target cell to achieve some therapeutic effect. Furthermore, since Applicant only speculates that all signal peptides will function as importation signal peptides, having demonstrated it only for Kaposi fibroblast growth factor, a skilled artisan will have to determine if any other known signal peptide can function as in importation signal. Since neither the prior art nor the specification provides the answers to all of these questions, it would require a large quantity of trial and error experimentation by the skilled artisan to do so.

Based on the broad scope of the claims, the unpredictability in the area of the invention, the lack of sufficient guidance or working examples in the specification and the quantity of experimentation necessary, it would clearly require undue

experimentation by one of skill in the art to determine how to use the claimed methods of importing a biologically active molecule into a cell of a subject for therapeutic purposes.

8. Claim 8 is rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This rejection is based on the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. §112, first paragraph "Written Description" Requirement published in the Federal Register (Volume 66, Number 4, Pages 1099-1111). Claim 8 is drawn to a method of importing a biologically active molecule wherein the molecule is a therapeutic agent. This is a genus claim in terms of any therapeutic agent. The specification mentions cancer drugs and toxic chemicals. This disclosure is not deemed to be descriptive of the complete structure of a representative number of species encompassed by the claims as one of skill in the art cannot envision all the therapeutic agents based on the teachings in the specification. "Cancer drugs" and 'toxic chemicals" encompass an enormous number of species. The specification does not teach any specific structure-function relationship among these species. Therefore, the specification does not describe the claimed therapeutic agents in such full, clear, concise and exact terms so as to indicate that Applicant has possession of these agents at the time of filing the present application. Thus, the written description requirement has not been satisfied.

9. Claims 6-15 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This rejection is based on the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. §112, first paragraph "Written Description" Requirement published in the Federal Register (Volume 66, Number 4, Pages 1099-1111). Claims 6 and 11 are drawn to a method of importing a biologically active molecule into a cell by linking the molecule to a importation competent signal peptide. These are genus claims in terms of any importation competent signal peptide. The specification mentions SEQ ID NO. 5, the signal peptide from Kaposi fibroblast growth factor. This disclosure is not deemed to be descriptive of the complete structure of a representative number of species encompassed by the claims as one of skill in the art cannot envision all importation competent signal peptides based on the teachings in the specification. The specification defines an importation competent signal peptide as a peptide that is about 10 to about 50 or more amino acids, comprises a hydrophobic portion, and is capable of penetrating through a cell membrane to allow export of cellular proteins and that the invention has shown that these signal peptides are importation competent as well (p. 10, lines 24-p. 11, lines 2). The specification further states that amino acid sequences may be mutated or modified as long as the translocation-mediating function of the peptide is not affected and also speculates that signal peptides may be mutated such that they lost the ability to export a protein but

maintain the ability to import molecules (p. 11, lines 2-11). The specification does not teach a correlation between any particular structural features of SEQ ID No. 5 and its importation function. There are no teachings about which specific sequences are related only to import function vs export function. Therefore, the specification does not describe the claimed importation competent signal peptides in such full, clear, concise and exact terms so as to indicate that Applicant has possession of these peptides at the time of filing the present application. Thus, the written description requirement has not been satisfied.

Conclusion

Claims 6-15 are rejected.

Certain papers related to this application may be submitted to Art Unit 1636 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014. NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bronwen M. Loeb whose telephone number is (703) 605-1197. The examiner can normally be reached on Monday through Friday, from 10:00 AM to 6:30 PM. A phone message left at this number will be responded to as soon as possible (usually no later than the next business day after receipt by the examiner).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel, can be reached on (703) 305-1998.

Any inquiry of a general nature or relating to the status of this application should be directed to Tracey Johnson, Patent Analyst whose telephone number is (703) 305-2982.

Bronwen M. Loeb, Ph.D.
Patent Examiner
Art Unit 1636

June 2, 2002

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